# Safety and efficacy of influenza vaccination in lung transplant recipients

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The London Olympic Games have recently ended with a great Closing Ceremony, and while some of us might still be in denial, the Olympic idea lives on. The focus is now on Rio de Janeiro in 2016! The Olympic motto *Citius, Altius, Fortius* (faster, higher, stronger) remains relevant in a number of spheres. Pierre de Coubertin, the father of the modern Olympic Games, expressed his thoughts in the Olympic creed: "The most important thing in the Olympic Games is not to win but to take part, just as the most important thing in life is not the triumph but the struggle...."

In the field of transplantation, the ongoing struggle is to balance the risks of allograft rejection and infection with the benefits of living a normal life following transplantation, a challenge transplant patients face nearly every day. In particular, infectious complications within the first year after lung transplantation account for significant morbidity and mortality.[1,2] A recent pediatric study showed an incidence of respiratory viral infection of 14% in the first year after lung transplantation.[3] The incidence of respiratory viral infections in symptomatic adult lung transplant recipients (LTRs) ranges from 35-66%.[4] Thus, prevention of viral infections is paramount, and the basis for prevention is adequate vaccination if available.

Following the global 2009 H1N1 influenza virus pandemic, recommendations regarding the diagnosis, prevention and therapy of influenza were issued by the American Society of Transplantation, in view of the risk of severe influenza infection and influenza-related complications in solid organ transplant recipients (SOTRs).[5] A specific concern in LTRs is the potential association between respiratory viral infections and acute allograft rejection and the subsequent development of bronchiolitis obliterans syndrome (BOS). A recent literature review by Vu et al investigating the relationship between viral respiratory infection and graft complications in adult LTRs did not conclusively support an association between respiratory viral infection and acute lung rejection and the subsequent development of BOS, mainly due to the heterogeneity and the retrospective design of published studies to date.[6] In the pediatric lung transplant population, respiratory viral infection has been associated with a 2.5-fold decrease in 1-year survival but it was not linked with the development of BOS in retrospective studies.[3,7] Failure to demonstrate a relationship however should not be misconstrued as evidence of the lack of a causal link. Hence, a National Institutes of Health study in pediatric lung transplantation is currently underway to investigate the potential interaction between respiratory viral infections and BOS utilizing improved

molecular diagnostics for respiratory viruses and increased patient surveillance (https://www.ctotc.org/).

Usually, transplant centers recommend LTRs receive vaccination with the annual influenza vaccine from as early as 3-6 months post-transplant; however, there is a lack of data regarding the most suitable time point for vaccine administration and concerns exist about an impaired vaccine response.[8] Vaccine antibody response is usually used as a surrogate marker of vaccine efficacy; however, this is not equal with protection. Factors that lead to non-response in LTRs after influenza vaccination have yet to be established. A systemic review and meta-analysis assessing influenza vaccination for immunocompromised patients showed a significant effect in the prevention of an influenza-like illness and no consistent evidence of safety concerns or serious adverse events (AEs) after influenza vaccination.[9] A recent observational study from Zurich showed that nearly 50% of LTRs reported no AEs after H1N1 vaccination, with the remaining LTRs mostly having minor/moderate AEs, such as local reactions at the injection site.10 Serious and reportable AEs occurred in 6% of LTRs. The effectiveness of H1N1 vaccination was reported as >90% in the study; however, the effectiveness was only assessed based on protection from subsequent H1N1 infection and not on vaccine antibody response.

Even though the benefits of immunization have been shown, there is evidence that exposure to influenza antigens after vaccination might directly activate alloreactive T and B cells, an effect labelled "heterologous immunity".[11] Danziger-Isakov et al investigated effects of influenza immunization on humoral and cellular alloreactivity in healthy controls (N=30) and SOTRs (N=17), demonstrating that influenza vaccination induced virus-specific reactive humoral and cellular responses in both groups.[11] In a recent Swiss study in kidney transplant recipients de novo anti-HLA antibodies were detected using single antigen beads technology following one dose of seasonal influenza and two doses of adjuvanted influenza/H1N1 vaccines.[12] Antibodies were both donor-specific and non-donor-specific and mainly low level. However, in an accompanying editorial in the same edition of the American Journal of Transplantation, Kumar and Danziger-Isakov rightly point out that increased HLA alloantibody titers could potentially be due to sub-clinical or undiagnosed influenza infection during the H1N1 pandemic, and clinical rejection in two study patients could be explained by other factors.[13] Further, Kumar and Danziger-Isakov recommend that the study results of Katerinis should be interpreted with caution so as to balance any potential vaccination-associated risks with the well described benefits in disease prevention.

In conclusion, the benefits of influenza vaccination and its effectiveness in preventing viral disease seem to clearly outweigh the risks of vaccine-related AEs that are predominantly minor and self-limiting in nature. In view of the emerging evidence of the potential impact of influenza vaccination on recipients' alloresponse, further research is required to investigate its impact on long-term allograft function and the potential association with the development of BOS. As Pierre de Coubertin said, the essential thing is not to have conquered but to have fought well....

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**References:**


1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult lung and heart-lung transplant report—2011. J Heart Lung Transplant 2011: 30: 1104-1122
2. Benden C, Aurora P, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: fourteenth pediatric lung and heart-lung transplantation report—2011. J Heart Lung Transplant 2011: 30: 1123-1132
3. Liu M, Worley S, Arrigain S, et al. Respiratory viral infections within one year after pediatric lung transplant. Transpl Infect Dis 2009; 11: 304-312
4. Benden C, Danziger-Isakov LA, Faro A. New developments in treatment after lung transplantation. Curr Pharm Des 2012; 18: 737-746
5. Kumar D, Morris M, Fischer S, et al. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. Am J Transplant 2010; 10: 18-25
6. Vu DL, Bridevaux PO, Aubert JD, et al. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. Am J Transplant 2011; 11: 1071-1078
7. Liu M, Mallory GB, Schecter MG, et al. Long-term impact of respiratory viral infection after pediatric lung transplantation. Pediatr Transplant; 14: 431-436
8. Danziger-Isakov LA, Husain S, Mooney ML, et al. The novel 2009 H1N1 influenza virus pandemic: unique considerations for programs in cardiothoracic transplantation. J Heart Lung Transplant 2009; 28: 1341-1347
9. Beck CR, McKenzie BC, Hashim AB, et al. Influenza vaccination for immunocompromised patients: systemic review and meta-analysis from a public health policy perspective. PLoS One 2011; 6: e:29249
10. Schuurmans MM, Tini GM, Dalar L, et al. Pandemic 2009 H1N1 influenza virus vaccination in lung transplant recipients: coverage, safety and clinical effectiveness in the Zurich cohort. J Heart Lung Transplant 2011; 30: 685-690
11. Danziger-Isakov L, Cherkassy L, Siegel H, et al. Effects of influenza immunization on humoral and cellular alloreactivity in humans. Transplantation 2010; 89; 838-844
12. Katerinis I, Hadaya K, Duquesnoy R, et al. De novo anti-HLA antibody after pandemic H1N1 and seasonal influenza immunization in kidney transplant recipients. Am J Transplant 2011; 11: 1727-1733